

REMARKS

Claims 21-22, 35-36 and 40-55 are pending in this application. Claims 1-20, 23-34, 37-39 and 56-61 have been canceled without prejudice. Reconsideration is respectfully requested.

THE INVENTION

The present invention provides novel compounds and compositions that advantageously enhance the delivery of therapeutic or diagnostic agents to a cell or tissue. Included among the therapeutic and diagnostic agents that can be delivered are proteins and nucleic acids, including gene therapy vectors.

REJECTION UNDER 35 U.S.C. § 112, first paragraph

Claims 1-55 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly including subject matter that was not described in the specification in such a way as to enable one of skill in the art to make and/or use the invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

In order to expedite prosecution, Applicants have canceled claims 1-20, 23-34, 37-39 and 56-61. As to these canceled claims, the rejection has been rendered moot. Applicants believe that these claims are fully enabled and have canceled these claims without prejudice to re-entry of the claims in a continuation application.

Applicants are now only claiming new and unobvious compounds and therefore, the enablement rejection appears misplaced. Clearly, the specification teaches how to make and use the new compounds of the present invention. In fact, the specification provides examples of how to make and use the compounds of Formula I. For instance, Example 12 teaches how to synthesize the compounds of Formula I. Further, Example 11 teaches how to isolate compounds of Formula I from Big CHAP. Moreover, Applicants teach how to use the compounds of the present invention in Example 11. Therefore, Applicants respectfully request that the Examiner withdraw the enablement rejection.

REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1, 7, 12, 16, 23, 29, 41-42, 45, 54 and 55 stand rejected under 35 USC § 102(b) as allegedly being anticipated by Aungst *et al.*, *Int. J. Pharm.*, (1993) 53: 227-235 ("Aungst *et al.*"). The cited reference discusses delivery of insulin in a formulation that includes Big CHAP. Although Big CHAP is not encompassed by the formulas set forth in Applicants' claims, the rejection asserts that the Big CHAP taught by Aungst *et al.* inherently contains the

compounds of Formula I. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection. More particularly, as explained below, Applicants respectfully state that the Examiner is using the improper test in formulating the anticipation rejection.

A compound that is purer than a previously known mixture containing the compound is patentable. A long line of cases in the Court of Customs and Patent Appeals has adopted the rule that simply stated, is whether the prior art suggests the particular pure structure or form of the compound or composition as well as suitable methods of obtaining that structure or form (*see, In re Bergstrom*, 427 F.2d 1394, 166 USPQ 256 (CCPA 1970); *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966); *In re Seaborg*, 328 F.2d 996, 140 USPQ 662 (CCPA 1964); cf. *In re Williams*, 171 F.2d 319, 80 USPQ 150 (CCPA 1948)).

For example, in *In re Cofer*¹, Appellants crystallized a known thermosetting epoxy resin known as 2,2B. The prior art had shown that 2,2B was known, but characterized the compound as a viscous liquid. The prior art had indicated that 2,2B was useful as an epoxy resin and as a stabilizer for resins. The court stated:

[w]e think examination of the decisions ... will demonstrate that the materials involved therein were found unpatentable where the alleged difference in form or purity of those substances was either disclosed or inherent in, or rendered obvious by, the prior art of record. ... To be sure, whether a given chemical compound or composition has the same usefulness as closely related materials may be an important consideration in determining obviousness under 35 U.S.C. § 103 . But it is only one consideration ... [O]ther acts [include] ... *whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form*. [Emphasis added]².

Similarly, in *In re Bergstrom*³, Appellants isolated 2 chemical compounds (prostaglandins) in essentially pure crystalline form from “crude materials” (prostate glands and sperm). The record showed that scientists had known for many years that extracts obtained from human and animal male accessory genital glands possessed the pharmacodynamic effects of lowering blood pressure and stimulating smooth muscle. The purified compounds were found to have a smooth muscle stimulating effect and one had hypotensive activity. The court stated:

[T]he criteria for determining whether given subject matter is “new” within the meaning of § 101 are no different than the criteria for determining whether that subject matter possesses the “novelty”

¹ *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966).

² *Id.* at 354 F.2d at 667-68, 148 USPQ at 271.

³ *In re Bergstrom*, 427 F.2d 1394, 166 USPQ 256 (CCPA 1970).

expressed in the title of § 102. The word "new" in § 101 is defined and is to be construed in accordance with the provision of § 102. ... *[B]y definition, pure materials necessarily differ from less pure or impure materials and, if the latter are the only ones existing and available as a standard of reference ... perforce the "pure" materials are "new" with respect to them. ... [W]hether the claimed pure materials have the same usefulness or assortment of properties as the impure materials of the prior art ... is a question having no bearing on the factual and legal matter whether the pure materials are new vis-a-vis impure materials within the meaning of § 101, although it is but one of the factors to be considered in determining their obviousness under 35 U.S.C. § 103⁴. [Emphasis added.]*

Likewise, in *In re Seaborg*,⁵ the Examiner had rejected Appellants claim to Element 95 stating that Element 95 must be inherently produced in the operation of a Fermi reactor. The court stated:

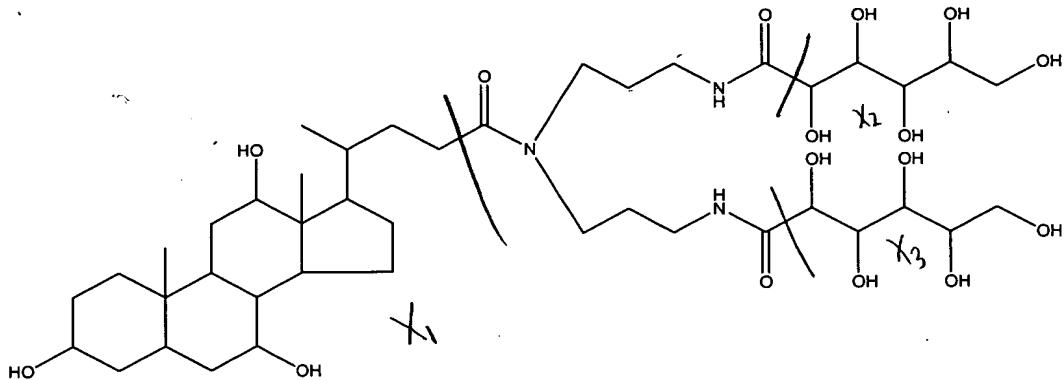
[t]he record before us unlike the record in the Wiegand case, is replete with a showing that the claimed product, if it was produced in the Fermi process, was produced in such a minuscule amounts and under such conditions that its presence was undetectable.

Thus, the Examiner's rejection based upon inherency is misplaced. Under *In re Bergstrom*, 427 F.2d 1394, 166 USPQ 256 (CCPA 1970) *supra*; *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) *supra*; and *In re Seaborg*, 328 F.2d 996, 140 USPQ 662 (CCPA 1964) *supra*, the test becomes "whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form." Thus, under the applicable case law, the anticipation rejection becomes, in essence, an obviousness question. Applicants assert that nothing in the prior art teaches or suggest the compounds of Formula I. Aungst *et al.* do not teach or suggest that Big CHAP has impurities. Further, Aungst *et al.* do not teach or suggest the use of Big CHAP impurities. Aungst *et al.* do not teach or suggest a method of making the compounds of Formula I.

Aungst *et al.* teach that Big CHAP is N,N-Bis(3-D-gluconamidopropyl)cholamide on page 228, second column. N,N-Bis(3-D-gluconamidopropyl)cholamide has the chemical structure below:

⁴ *Id.* at 427 F.2d at 1401-02, 166 USPQ at 262.

⁵ 328 F.2d 996, 140 USPQ 662 (CCPA 1964).



As depicted above, Big CHAP has a chemical formula wherein the cholic acid functional group is attached to an amide bond wherein the nitrogen of the amide bond is disubstituted. In stark contrast, the compound of formula I sets forth compound wherein X_1 is a cholic acid group or deoxycholic acid group that is attached to an amide bond that is monosubstituted. Further, in certain preferred embodiments, the compounds of the instant claims have two cholic acid groups. There is simply no teaching or suggestion of two cholic acid groups in the Big CHAP compound of Aungst *et al.*

However, even if the Big CHAP as taught by Aungst *et al.* contained the impurity as set forth in Formula I, *and Applicants maintain there is no evidence for such impurity*, under the applicable case law, pure materials necessarily differ from less pure or impure materials and, if the latter are the only ones existing and available as a standard of reference ... perforce the "pure" materials are "new" with respect to them.

Moreover, whether the prior art suggests the particular structure or form of the compound or composition is but the first step of the inquiry. The second step is whether the prior art discloses a suitable method of obtaining that structure or form. Applicants assert that Aungst *et al.* do not teach or suggest the compounds set forth in Formula I nor do they teach a method of producing it. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejection.

REJECTION UNDER 35 U.S.C. § 103

Claims 1-6, 8, 12-15, 17, 23-26, 30 and 39-40 stand rejected under 35 USC § 103(a) as allegedly being obvious over Aungst *et al.* (*Int. J. Pharm.* (1993) 53: 227-235) in view of Carson *et al.* (U.S. Patent No. 5,804,566, issued September 8, 1998 and filed November 1, 1994). The Examiner states on page 7 in Paper No. 12:

The formulations in claims 42-53 are impurities also found in BigChap as taught by Aungst *et al.* and are obvious variations of the Formula I (claim 41) found in BigChap. Formula II (claim 54) is an impurity found in BigChap as

taught by Aungst *et al.* and the variation in claim 55 is an obvious variant of Formula II.

To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143, “[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).”

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

1. There is no Suggestion or Motivation to Modify the References

Applicants state that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Examiner has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicants assert that there is simply no motivation to make the modifications that the Examiner contemplates. Prior to the advent of the present invention, the structures and compounds of the instant claims were UNKNOWN. The Examiner states that the compounds in claims 42-53 are obvious variants of the unknown impurities, whose structures were unknown. Applicants believe there cannot be obvious variants of structurally unknown compounds. Without an unequivocal structure determined by organic structure analysis, an unknown compound cannot have an obvious variant.

Carson *et al.* do not supply the teaching that is lacking in the primary reference. Carson *et al.* teach methods for introducing biologically active peptides into a host by administration of polynucleotides which operatively encode for the peptide of interest. A mammal is desensitized to an antigen, in particular an allergen, through administration to the mammal of polynucleotides, which operatively encode the antigen. The antigen-encoding polynucleotides are administered to host tissues, which have a high concentration of antigen presenting cells. There is absolutely no teaching or suggestion of N,N-Bis(3-D-gluconamidopropyl)cholamide or impurities thereof in Carson *et al.*

As obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so, a *prima facie* obviousness rejection is untenable.

Moreover, Applicants maintain that inherency is improper under 35 U.S.C. § 103. The Examiner has cited as authority *In re Skoner*⁶. However, the facts in *In re Skoner* are inapposite to the facts of present invention. In *In re Skoner*, the prior art patent taught identical means (wire brushing) to achieve the same results (improved adhesion) as Appellants' invention. The Court stated:

perhaps the [Examiner's] rejection should have been made under §102 instead of §103. However, this court has sanctioned the practice of rejections on §103 when, in fact, the actual ground of rejection is that the claims are anticipated by the prior art.⁷

Thus, the court believed in fact that the Examiner's rejection was an anticipation rejection, but allowed the rejection because anticipation is the epitome of obviousness. Therefore, in view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection.

2. There is No Reasonable Expectation of Success

In addition, there is no reasonable expectation of success that the modification that the Examiner contemplates will succeed. "Both the suggestion and the expectation of success must be found in the prior art, not the Applicants' disclosure." *In re Dow Chem. Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

Applicants assert that there is absolutely no teaching or suggestion in the cited art to modify the teaching therein to arrive at the presently claimed invention. Rather, the Examiner

⁶ *In re Skoner*, 186 U.S.P.Q. 80.

⁷ *Id.* at 82, bottom.

has used the Applicants' disclosure as a blueprint to pick and choose features from the prior art in an attempt to reconstruct the presently claimed invention.

There is no reasonable expectation that the modification that the Examiner contemplates will succeed. The Examiner states:

The formulations in claims 42-53 are impurities also found in BigChap as taught by Aungst *et al.* and are obvious variations of the Formula I (claim 41) found in BigChap. Formula II (claim 54) is an impurity found in BigChap as taught by Aungst *et al.* and the variation in claim 55 is an obvious variant of Formula II.

However, Aungst *et al.* do not teach or suggest that Big CHAP has impurities. Further, Aungst *et al.* do not teach or suggest the use of Big CHAP impurities. Aungst *et al.* do not teach or suggest a method of making the compounds of Formula I. Applicants assert that a skilled person in view of Aungst *et al.*, would have no expectation of making obvious variants of structurally UNKNOWN compounds. The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. *In re Shetty*, 566 F.2d 81, 195 USPQ 753, 757 (CCPA 1977). Thus, the Examiner has used hindsight reconstruction of the cited art in an attempt to piece together the present invention. Hindsight reconstruction is impermissible and therefore, Applicants respectfully request that the Examiner withdraw the rejection.

3. The Cited Art References Do Not Teach All Limitations of the Claims

The prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants assert that the prior art references do not teach or suggest all the limitations of the claims and therefore, the obviousness rejection is untenable.

Applicants claim novel unobvious compounds. Under *In re Wilson* *supra*, a *prima facie* case of obviousness has not been established because each of the limitation of the claims is not taught or suggested in the cited art references. Aungst *et al.* do not teach or suggest that Big CHAP has impurities. Aungst *et al.* do not teach or suggest the use of Big CHAP impurities. Further, Aungst *et al.* do not teach the structural limitations of the compounds as presently claimed. Therefore, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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